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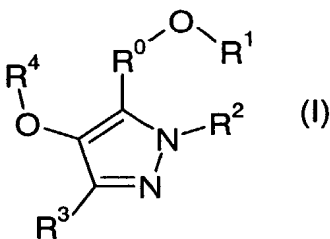
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(54) Title: PYRAZOLE DERIVATIVES AND THEIR USE AS THERAPEUTIC AGENTS FOR HIV MEDIATED DISEASES



(57) Abstract: This invention relates to pyrazole derivatives of formula (I) or pharma-
ceutically acceptable salts, solvates or derivative thereof, wherein R¹ to R⁴; are defined
in the description, and to processes for the preparation thereof, intermediates used in
their preparation of, compositions containing them and the uses of such derivatives.
The compounds of the present invention bind to the enzyme reverse transcriptase and
are modulators, especially inhibitors thereof. As such the compounds of the present
invention are useful in the treatment of a variety of disorders including those in which
the inhibition of reverse transcriptase is implicated. Disorders of interest include those
caused by Human Immunodeficiency Virus (HIV) and genetically related retroviruses,
such as Acquired Immune Deficiency Syndrome (AIDS).

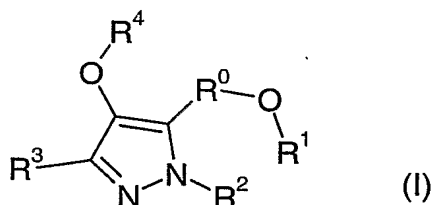
PYRAZOLE DERIVATIVES AND THEIR USE AS THERAPEUTIC AGENTS FOR HIV MEDIATED DISEASES

This invention relates to pyrazole derivatives, to their use in medicine, to compositions containing them, to processes for their preparation and to intermediates used in such processes.

Reverse transcriptase is implicated in the infectious lifecycle of Human Immunodeficiency Virus (HIV). Compounds which interfere with the function of this enzyme have shown utility in the treatment of conditions caused by HIV and genetically related retroviruses, such as Acquired Immune Deficiency Syndrome (AIDS). There is a constant need to provide new and better modulators, especially inhibitors, of HIV reverse transcriptase, since the virus is able to mutate, becoming resistant to the effects of known modulators.

Antiviral activity is ascribed to a class of N(hydroxyethyl)pyrazole derivatives in US patent number 3,303,200. A number of pyrazoles are disclosed as reverse transcriptase inhibitors, including: a class of N-phenylpyrazoles (*J. Med. Chem.*, 2000, **43**, 1034); a class of C and S linked aryl pyrazoles (WO02/04424); and a class of O and S linked aryl pyrazoles, the O and S aryl link being adjacent to the nitrogen atom (WO02/30907).

According to the present invention there is provided a compound of formula (I)



25

or a pharmaceutically acceptable salt, solvate or derivative thereof, wherein:

R^0 is absent or C_1 - C_6 alkylene;

R^1 is phenyl substituted by $-\text{SO}_y\text{R}^5$, $-(C_1\text{-}C_6 \text{ alkylene})-\text{SO}_y\text{R}^5$, $-\text{SO}_y\text{CF}_3$, $-(C_1\text{-}C_6 \text{ alkylene})-\text{SO}_y\text{CF}_3$, $-\text{CO}_2\text{R}^5$, $-(C_0\text{-}C_6 \text{ alkylene})-\text{CO}_2\text{R}^5$, OCF_3 , a five or six-membered aromatic heterocyclic group containing (i) from 1 to 4 nitrogen heteroatom(s) or (ii) 1 or 2 nitrogen heteroatom(s) and 1 oxygen or 1 sulphur heteroatom (said heterocyclic group being optionally substituted by halo, oxo, $-\text{CN}$, $-\text{COR}^5$, $-\text{CO}_2\text{R}^5$, $-\text{CONR}^5\text{R}^5$, $-\text{SO}_y\text{R}^5$, $-\text{SO}_y\text{CF}_3$, $-\text{SO}_2\text{NR}^5\text{R}^5$, $-\text{NR}^5\text{SO}_2\text{R}^5$,

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-OR⁵, -OCF₃, -NR⁵R⁵, -(C₁-C₆ alkylene)-NR⁵R⁵, C₁-C₆ alkyl, fluoro(C₁-C₆)alkyl or C₃-C₇ cycloalkyl), said phenyl being optionally additionally substituted by halo, -CN, -COR⁵, -CONR⁵R⁵, -SO₂NR⁵R⁵, -NR⁵SO₂R⁵, -OR⁵, -NR⁵R⁵, -(C₁-C₆ alkylene)-NR⁵R⁵, C₁-C₆ alkyl, halo(C₁-C₆)alkyl or C₃-C₇ cycloalkyl; or,
 5 when R⁰ is C₁-C₆ alkylene, R¹ may also be a five or six-membered aromatic heterocyclic group containing (i) from 1 to 4 nitrogen heteroatom(s) or (ii) 1 or 2 nitrogen heteroatom(s) and 1 oxygen or 1 sulphur heteroatom or (iii) 1 or 2 oxygen or sulphur heteroatom(s), said heterocyclic group being optionally substituted by halo, oxo, -CN, -COR⁵, -CONR⁵R⁵, -SO₂NR⁵R⁵, -NR⁵SO₂R⁵, -OR⁵,
 10 -OR¹¹, -NR⁵R⁵, -(C₁-C₆ alkylene)-NR⁵R⁵, R⁷ or R¹¹;

R² is H, C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkenyl, phenyl, benzyl, R⁸ or R⁹, said C₁-C₆ alkyl, C₃-C₇ cycloalkyl, phenyl and benzyl being optionally substituted by halo, -OR⁵, -OR¹⁰, -CN,
 15 -CO₂R⁷, -OCONR⁵R⁵, -CONR⁵R⁵, -C(=NR⁵)NR⁵OR⁵, -CONR⁵NR⁵R⁵, -NR⁶R⁶, -NR⁵R¹⁰, -NR⁵COR⁵, -NR⁵COR⁸, -NR⁵COR¹⁰, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁵, -SO₂NR⁵R⁵, -NR⁵SO₂R⁵, -NR⁵SO₂NR⁵R⁵, R⁸ or R⁹;

R³ is H, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, phenyl, benzyl, halo, -CN, -OR⁷, -CO₂R⁵,
 20 -CONR⁵R⁵, R⁸ or R⁹, said C₁-C₆ alkyl, C₃-C₇ cycloalkyl, phenyl and benzyl being optionally substituted by halo, -CN, -OR⁵, -CO₂R⁵, -CONR⁵R⁵, -OCONR⁵R⁵, -NR⁵CO₂R⁵, -NR⁶R⁶, -NR⁵COR⁵, -SO₂NR⁵R⁵, -NR⁵CONR⁵R⁵, -NR⁵SO₂R⁵, R⁸ or R⁹;

R⁴ is phenyl, naphthyl or pyridyl, each being optionally substituted by R⁸, halo, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₇ cycloalkyl, C₁-C₆ alkoxy, -CONR⁵R⁵, OR¹¹, SO_xR⁶, O-(C₁-C₆ alkylene)-CONR⁵R⁵, O-(C₁-C₆ alkylene)-NR⁵R⁵, or O-(C₁-C₆ alkylene)-OR⁶;

each R⁵ is independently either H, C₁-C₆ alkyl or C₃-C₇ cycloalkyl or, when two R⁵ groups are attached to the same nitrogen atom, those two groups taken together with the nitrogen atom to which they are attached represent azetidiny, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl or morpholinyl, said azetidiny, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl,
 35 homopiperazinyl and morpholinyl being optionally substituted by C₁-C₆ alkyl or C₃-C₇ cycloalkyl;

each R⁶ is independently either H, C₁-C₆ alkyl or C₃-C₇ cycloalkyl;

R^7 is C_1 - C_6 alkyl or C_3 - C_7 cycloalkyl;

R^8 is a five or six-membered, aromatic heterocyclic group containing (i) from 1 to 4 nitrogen heteroatom(s) or (ii) 1 or 2 nitrogen heteroatom(s) and 1 oxygen or 1 sulphur heteroatom or (iii) 1 or 2 oxygen or sulphur heteroatom(s), said heterocyclic group being optionally substituted by halo, oxo, -CN, -COR⁵, -CONR⁵R⁵, -SO₂NR⁵R⁵, -NR⁵SO₂R⁵, -OR⁵, -NR⁵R⁵, -(C₁-C₆ alkylene)-NR⁵R⁵, C₁-C₆ alkyl, fluoro(C₁-C₆)alkyl or C₃-C₇ cycloalkyl;

R^9 is a four to seven-membered, saturated or partially unsaturated heterocyclic group containing (i) 1 or 2 nitrogen heteroatom(s) or (ii) 1 nitrogen heteroatom and 1 oxygen or 1 sulphur heteroatom or (iii) 1 oxygen or sulphur heteroatom, said heterocyclic group being optionally substituted by oxo, C₁-C₆ alkyl, C₃-C₇ cycloalkyl, -SO₂R⁵, -CONR⁵R⁵, -COOR⁵, -CO-(C₁-C₆ alkylene)-OR⁵ or -COR⁵ and optionally substituted on a carbon atom which is not adjacent to a heteroatom by halo, -OR⁵, -NR⁵R⁵, -NR⁵COR⁵, -NR⁵COOR⁵, -NR⁵CONR⁵R⁵, -NR⁵SO₂R⁵ or -CN;

R^{10} is C₁-C₆ alkyl substituted by R⁸, R⁹, -OR⁵, -CONR⁵R⁵, -NR⁵COR⁵ or -NR⁵R⁵;

R^{11} is phenyl optionally substituted by halo, -CN, -COR⁵, -CONR⁵R⁵, -SO₂NR⁵R⁵, -NR⁵SO₂R⁵, -OR⁵, -NR⁵R⁵, -(C₁-C₆ alkylene)-NR⁵R⁵, C₁-C₆ alkyl, halo(C₁-C₆)alkyl or C₃-C₇ cycloalkyl; and

x and y are independently 0, 1 or 2.

In the above definitions, halo means fluoro, chloro, bromo or iodo. Unless otherwise stated, alkyl, alkenyl, alkynyl, alkylene and alkoxy groups containing the requisite number of carbon atoms can be unbranched or branched chain. Examples of alkyl include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. Examples of alkenyl include ethenyl, propen-1-yl, propen-2-yl, propen-3-yl, 1-buten-1-yl, 1-buten-2-yl, 1-buten-3-yl, 1-buten-4-yl, 2-buten-1-yl, 2-buten-2-yl, 2-methylpropen-1-yl or 2-methylpropen-3-yl. Examples of alkynyl include ethynyl, propyn-1-yl, propyn-3-yl, 1-butyne-1-yl, 1-butyne-3-yl, 1-butyne-4-yl, 2-butyne-1-yl. Examples of alkylene include methylene, 1,1-ethylene, 1,2-ethylene, 1,1-propylene, 1,2-propylene, 2,2-propylene and 1,3-propylene. Examples of alkoxy include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy and t-butoxy. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Where a heterocyclic group

R¹, R⁸ or R⁹ is attached to an oxygen, sulphur or nitrogen heteroatom the heterocyclic group R¹, R⁸ or R⁹ must be linked through a ring carbon atom.

5 The pharmaceutically acceptable salts of the compounds of formula (I) include the acid addition and the base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, chloride, bromide, iodide, sulphate, bisulphate, nitrate, phosphate, hydrogen phosphate, acetate, fumarate, pamoate, aspartate, besylate, carbonate, bicarbonate/, camsylate, D and L-lactate, D and L-tartrate, esylate, mesylate, malonate, orotate, gluceptate, methylsulphate, stearate, glucuronate, 2-napsylate, tosylate, hibenzate, nicotinate, isethionate, malate, maleate, citrate, gluconate, succinate, saccharate, benzoate, esylate, and pamoate salts.

15 Suitable base salts are formed from bases which form non-toxic salts and examples are the sodium, potassium, aluminium, calcium, magnesium, zinc, choline, diolamine, olamine, arginine, glycine, tromethamine, benzathine, lysine, meglumine and diethylamine salts.

20 For reviews on suitable salts see Berge *et al*, J. Pharm. Sci., **66**, 1-19, 1977 and Bighley *et al*, Encyclopedia of Pharmaceutical Technology, Marcel Dekker Inc, New York, 1996, Vol 13, pp453-497

25 The pharmaceutically acceptable solvates of the compounds of formula (I) include the hydrates thereof.

The compound of formula (I) may be modified to provide pharmaceutically acceptable derivatives thereof at any of the functional groups in the compound. Examples of such derivatives are described in: Drugs of Today, Volume 19, Number 9, 1983, pp 499 – 538; Topics in Chemistry, Chapter 31, pp 306 – 316; and in "Design of Prodrugs" by H. Bundgaard, Elsevier, 1985, Chapter 1 (the disclosures in which documents are incorporated herein by reference) and include: esters, carbonate esters, hemi-esters, phosphate esters, nitro esters, sulfate esters, sulfoxides, amides, sulphonamides, carbamates, azo-compounds, phosphamides, glycosides, ethers, acetals and ketals.

The invention encompasses all isomers of the compound of formula (I) and pharmaceutically acceptable salts, solvates or derivatives thereof, including all

geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures).

5 Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation, chromatography or high performance liquid chromatography (HPLC) of a stereoisomeric mixture of compounds. An individual enantiomer of a compound may also be prepared from a corresponding optically pure intermediate or by resolution, such as by HPLC of the corresponding racemate using a suitable chiral support, or by fractional
10 crystallisation of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate.

15 The compound of formula (I) and pharmaceutically acceptable salts, solvates or derivatives thereof may have the ability to crystallize in more than one form, a characteristic known as polymorphism, and all such polymorphic forms ("polymorphs") are encompassed within the scope of the invention. Polymorphism generally can occur as a response to changes in temperature or pressure or both, and can also result from variations in the crystallization
20 process. Polymorphs can be distinguished by various physical characteristics, and typically the x-ray diffraction patterns, solubility behaviour, and melting point of the compound are used to distinguish polymorphs.

25 Compounds of formula (I), pharmaceutically acceptable salts, solvates and derivatives thereof, isomers thereof, and polymorphs thereof, are hereinafter referred to as the compounds of the invention.

Preferred compounds of the invention are the compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof.

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Preferably, R^0 is C_1 - C_6 alkylene.

Preferably, R^0 is C_1 - C_3 alkylene.

Preferably, R^0 is ethylene.

35 Preferably, R^1 is phenyl substituted by $-SO_yR^5$, $(C_1-C_6 \text{ alkylene})-SO_yR^5$, $-SO_yCF_3$, $-(C_1-C_6 \text{ alkylene})-SO_yCF_3$, $-CO_2R^5$, $-(C_0-C_6 \text{ alkylene})-CO_2R^5$ or OCF_3 , a five or six-membered aromatic heterocyclic group containing (i) from 1 to 4 nitrogen heteroatom(s) or (ii) 1 or 2 nitrogen heteroatom(s) and 1 oxygen or 1 sulphur heteroatom (said heterocyclic group being optionally substituted by halo, oxo,

- CN, -COR⁵, -CO₂R⁵, -CONR⁵R⁵, -SO_yR⁵, -SO_yCF₃, -SO₂NR⁵R⁵, -NR⁵SO₂R⁵, -OR⁵, -OCF₃, -NR⁵R⁵, -(C₁-C₆ alkylene)-NR⁵R⁵, C₁-C₆ alkyl, fluoro(C₁-C₆)alkyl or C₃-C₇ cycloalkyl), said phenyl being optionally additionally substituted by halo, -CN, -COR⁵, -CONR⁵R⁵, -SO₂NR⁵R⁵, -NR⁵SO₂R⁵, -OR⁵, -NR⁵R⁵, -(C₁-C₆ alkylene)-NR⁵R⁵, C₁-C₆ alkyl, halo(C₁-C₆)alkyl or C₃-C₇ cycloalkyl.
- 5 Preferably, R¹ is phenyl substituted by -SO_yR⁵, (C₁-C₆ alkylene)-SO_yR⁵, -SO_yCF₃, -(C₁-C₆ alkylene)-SO_yCF₃, -CO₂R⁵, -(C₀-C₆ alkylene)-CO₂R⁵ or OCF₃, said phenyl being optionally additionally substituted by halo, -CN, -COR⁵, -CONR⁵R⁵, -SO₂NR⁵R⁵, -NR⁵SO₂R⁵, -OR⁵, -NR⁵R⁵, -(C₁-C₆ alkylene)-NR⁵R⁵, C₁-C₆ alkyl, halo(C₁-C₆)alkyl or C₃-C₇ cycloalkyl.
- 10 Preferably, R¹ is phenyl substituted by -SO_yR⁵, (C₁-C₆ alkylene)-SO_yR⁵, -CO₂R⁵, or -(C₀-C₆ alkylene)-CO₂R⁵, said phenyl being optionally additionally substituted by halo, -CN, -COR⁵, -CONR⁵R⁵, -SO₂NR⁵R⁵, -NR⁵SO₂R⁵, -OR⁵, -NR⁵R⁵, -(C₁-C₆ alkylene)-NR⁵R⁵, C₁-C₆ alkyl, halo(C₁-C₆)alkyl or C₃-C₇ cycloalkyl.
- 15 Preferably, R¹ is phenyl substituted by -SO_yR⁵, (C₁-C₆ alkylene)-SO_yR⁵, -CO₂R⁵, or -(C₀-C₆ alkylene)-CO₂R⁵.
- Preferably, R¹ is phenyl substituted by -SO_y(C₁-C₂ alkyl) or -(C₁-C₂ alkylene)-SO_y(C₁-C₂ alkyl).
- 20 Preferably, R² is H, C₁-C₆ alkyl, C₃-C₆ alkenyl, phenyl, benzyl or R⁹, said phenyl, benzyl or C₁-C₆ alkyl being optionally substituted by halo, -OR⁵, -OR¹⁰, -CN, -CO₂R⁷, -OCONR⁵R⁵, -CONR⁵R⁵, -C(=NR⁵)NR⁵OR⁵, -CONR⁵NR⁵R⁵, -NR⁶R⁶, -NR⁵R¹⁰, -NR⁵COR⁵, -NR⁵COR⁸, -NR⁵COR¹⁰, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁵, -SO₂NR⁵R⁵, -NR⁵SO₂R⁵, R⁸ or R⁹.
- 25 Preferably, R² is H C₁-C₆ alkyl, phenyl or benzyl, said C₁-C₆ alkyl being optionally substituted by halo, -OR⁵, -OR¹⁰ or -NH₂.
- Preferably, R² is H or C₁-C₃ alkyl optionally substituted by -OH or -NH₂.
- Preferably, R² is H.
- 30 Preferably, R³ is H, C₁-C₆ alkyl or C₃-C₇ cycloalkyl, said C₁-C₆ alkyl being optionally substituted by halo, -CN, -OR⁵, -CO₂R⁵, -CONR⁵R⁵, -OCONR⁵R⁵, -NR⁵CO₂R⁵, -NR⁶R⁶, -NR⁵COR⁵, -SO₂NR⁵R⁵, -NR⁵CONR⁵R⁵, -NR⁵SO₂R⁵, R⁸ or R⁹.
- Preferably, R³ is H, C₁-C₆ alkyl or C₃-C₇ cycloalkyl.
- 35 Preferably, R³ is H, C₁-C₃ alkyl or cyclopropyl.
- Preferably, R³ is methyl, ethyl or cyclopropyl.
- Preferably, R⁴ is phenyl optionally substituted by R⁸, halo, -CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₇ cycloalkyl or C₁-C₆ alkoxy.

Preferably, R^4 is phenyl substituted by R^8 , halo, -CN, C_1 - C_6 alkyl, or C_1 - C_6 alkoxy.
 Preferably, R^4 is phenyl substituted by halo, -CN, C_1 - C_6 alkyl, or C_1 - C_6 alkoxy.
 Preferably, R^4 is phenyl substituted by -CN.
 Preferably, R^4 is 3,5-dicyanophenyl.

5

Preferably, R^5 is H or C_1 - C_4 alkyl.
 Preferably, R^5 is C_1 - C_2 alkyl.

- 10 Preferably, R^8 is pyrrolyl, imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furanyl, thienyl, pyridinyl, pyridazinyl, pyrimidinyl or pyrazinyl, each being optionally substituted by halo, -CN, -COR⁵, -CONR⁵R⁵, -SO₂NR⁵R⁵, -NR⁵SO₂R⁵, -OR⁵, -NR⁵R⁵, -(C₁-C₆ alkylene)-NR⁵R⁵, C_1 - C_6 alkyl, fluoro(C_1 - C_6)alkyl or C_3 - C_7 cycloalkyl.
- 15 Preferably, R^8 is imidazolyl, pyrazolyl, 1,2,4-triazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridinyl, pyrazinyl or pyrimidinyl, each being optionally substituted by halo, -CN, -COR⁵, -CONR⁵R⁵, -SO₂NR⁵R⁵, -NR⁵SO₂R⁵, -OR⁵, -NR⁵R⁵, -(C₁-C₆ alkylene)-NR⁵R⁵, C_1 - C_6 alkyl, fluoro(C_1 - C_6)alkyl or C_3 - C_7 cycloalkyl.
- 20 Preferably, R^8 is imidazolyl, pyrazolyl, 1,2,4-triazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridinyl, pyrazinyl or pyrimidinyl, each being optionally substituted by -OR⁵, -NR⁵R⁵ or C_1 - C_6 alkyl.
- 25 Preferably, R^8 is imidazolyl, pyrazolyl, 1,2,4-triazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyridinyl, pyrazinyl or pyrimidinyl, each being optionally substituted by -OH, -NH₂ or methyl.

- 30 Preferably, R^9 is azetidiny, tetrahydropyrrolyl, piperidinyl, azepinyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, oxepinyl, morpholinyl, piperazinyl or diazepinyl, each being optionally substituted by oxo, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, -SO₂R⁵, -CONR⁵R⁵, -COOR⁵, -CO-(C₁-C₆ alkylene)-OR⁵ or -COR⁵ and optionally substituted on a carbon atom which is not adjacent to a heteroatom by halo, -OR⁵, -NR⁵R⁵, -NR⁵COR⁵, -NR⁵COOR⁵, -NR⁵CONR⁵R⁵, -NR⁵SO₂R⁵ or -CN.
- 35 Preferably, R^9 is azetidiny, piperidinyl, tetrahydrofuranyl, piperazinyl or morpholinyl, each being optionally substituted by oxo, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, -SO₂R⁵, -CONR⁵R⁵, -COOR⁵, -CO-(C₁-C₆ alkylene)-OR⁵ or -COR⁵ and optionally substituted on a carbon atom which is not adjacent to a heteroatom by halo, -OR⁵, -NR⁵R⁵, -NR⁵COR⁵, -NR⁵COOR⁵, -NR⁵CONR⁵R⁵, -NR⁵SO₂R⁵ or -CN.

Preferably, R^9 is azetidiny, piperidiny, tetrahydrofurany, piperaziny or morpholiny, each being optionally substituted by C_1 - C_6 alkyl, $-SO_2R^5$, $-CONR^5R^5$, $-COOR^5$, $-CO-(C_1-C_6 \text{ alkylene})-OR^5$ or $-COR^5$ and optionally substituted on a carbon atom which is not adjacent to a heteroatom by $-OR^5$ or $-NR^5COR^5$.

5 Preferably, R^9 is azetidiny, piperidiny, tetrahydrofurany, piperaziny or morphoniny, each being optionally substituted by $-CH_3$, $-SO_2CH_3$, $-CONH_2$, $-COOCH_3$, $-COCH_2OCH_3$ or $-COCH_3$ and optionally substituted on a carbon atom which is not adjacent to a heteroatom by $-OCH_3$ or $-NHCOCH_3$.

10 Preferably, R^{10} is C_1 - C_4 alkyl substituted by R^8 , R^9 , $-OR^5$, $-CONR^5R^5$, $-NR^5COR^5$ or $-NR^5R^5$.

Preferably, R^{10} is C_1 - C_4 alkyl substituted by R^9 , $-OR^5$, $-NR^5COR^5$ or $-NR^5R^5$.

Preferably, R^{10} is C_1 - C_2 alkyl substituted by tetrahydrofurany, $-OCH_3$, $-NHCOCH_3$ or $-NH_2$.

15

Preferably, R^{11} is phenyl substituted by halo, $-CN$, $-COR^5$, $-CONR^5R^5$, $-SO_2NR^5R^5$, $-NR^5SO_2R^5$, $-OR^5$, $-NR^5R^5$, $-(C_1-C_6 \text{ alkylene})-NR^5R^5$, C_1 - C_6 alkyl, halo(C_1 - C_6)alkyl or C_3 - C_7 cycloalkyl.

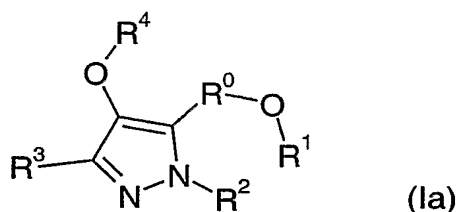
20 Preferably, R^{11} is phenyl substituted by halo, $-CN$, $-CONR^5R^5$, $-SO_2NR^5R^5$ or $-OR^5$.

Preferably, R^{11} is phenyl substituted by $-OR^5$.

Preferably, R^{11} is phenyl substituted by C_1 - C_2 alkoxy.

25 Preferred compounds according to the invention include all combinations of the preferred definitions for individual substituents given above.

Preferred compounds according to the invention include those of formula (Ia),



30

and pharmaceutically acceptable salts, solvates or derivatives thereof, wherein:

R^0 is C_1 - C_3 alkylene;

35 R^1 is phenyl substituted by $-SO_yR^5$, $(C_1-C_6 \text{ alkylene})-SO_yR^5$, $-CO_2R^5$, or $-(C_0-C_6 \text{ alkylene})-CO_2R^5$, said phenyl being optionally additionally substituted by

halo, -CN, -COR⁵, -CONR⁵R⁵, -SO₂NR⁵R⁵, -NR⁵SO₂R⁵, -OR⁵, -NR⁵R⁵,
 -(C₁-C₆ alkylene)-NR⁵R⁵, C₁-C₆ alkyl, halo(C₁-C₆)alkyl or C₃-C₇ cycloalkyl;

R² is H or C₁-C₃ alkyl optionally substituted by -OH or -NH₂;

R³ is H, C₁-C₃ alkyl or cyclopropyl;

5 R⁴ is phenyl substituted by halo, -CN, C₁-C₆ alkyl, or C₁-C₆ alkoxy;

R⁵ is H or C₁-C₄ alkyl; and

y is 0, 1 or 2.

10 Within the compounds of formula (Ia), preferably R¹ is phenyl substituted by
 -SO_yR⁵, (C₁-C₆ alkylene)-SO_yR⁵, -CO₂R⁵, or -C₀-C₆ alkylene)-CO₂R⁵

Preferred compounds of the invention are:

5-[(3-Ethyl-5-{2-[4-(methylsulfanyl)phenoxy]ethyl}-1*H*-pyrazol-4-
 yl)oxy]isophthalonitrile;

15 5-[(3-Ethyl-5-{2-[4-(methylsulfonyl)phenoxy]ethyl}-1*H*-pyrazol-4-
 yl)oxy]isophthalonitrile;

and pharmaceutically acceptable salts, solvates or derivatives thereof.

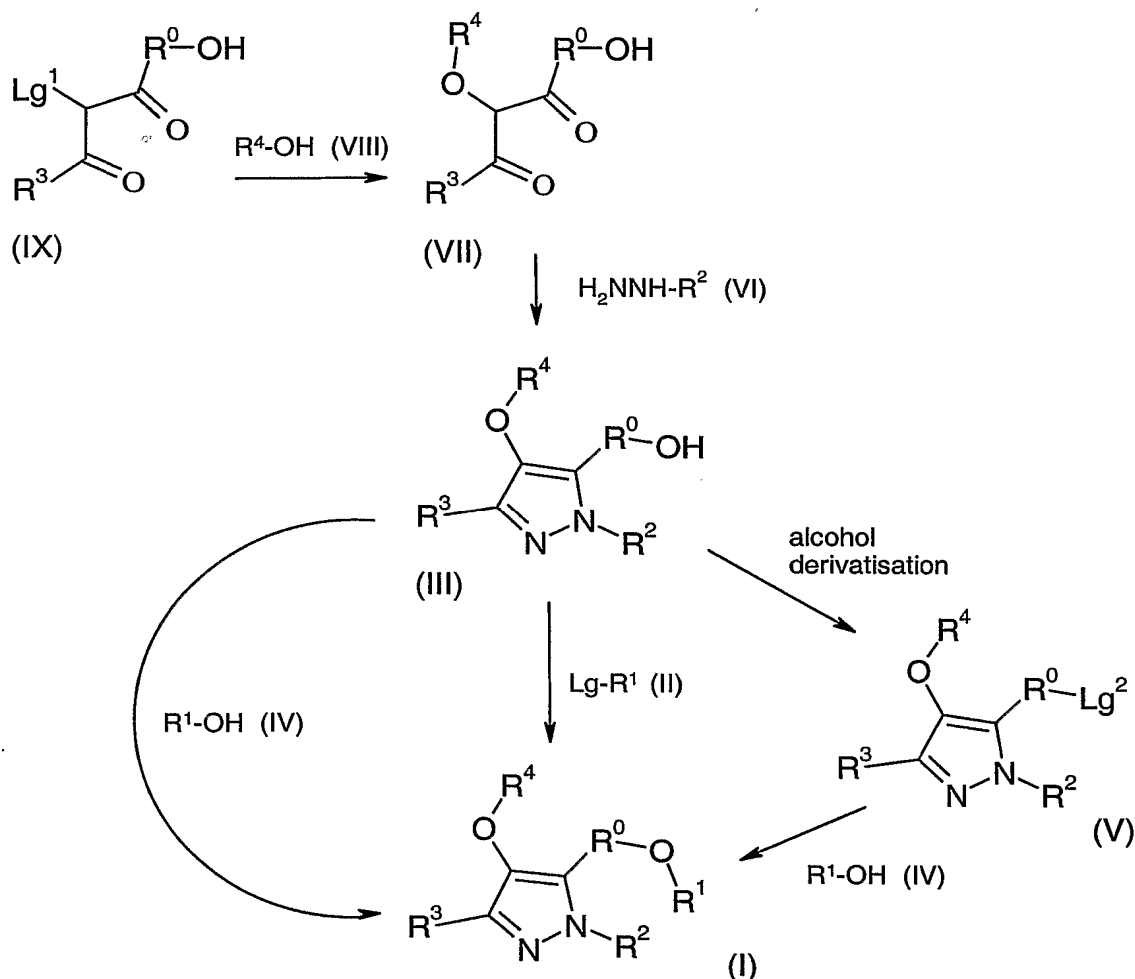
20 The compounds of the invention may have advantages over those of the prior art
 with regard to a number of useful properties or combination thereof, such as
 potency, duration of action, pharmacokinetics, spectrum of activity, side effect
 profile, solubility, chemical stability, and so on.

25 The compounds of the invention may be prepared by any method known in the
 art for the preparation of compounds of analogous structure. The compounds of
 the invention can be prepared by the procedures described in the methods
 below, or by the specific methods described in the Examples, or by similar
 methods to either. The invention also encompasses any one or more of these
 processes for preparing the compounds of the invention, in addition to any novel
 30 intermediates used therein.

35 In the following methods R⁰ to R⁴ are as previously defined for a compound of
 formula (I), unless otherwise stated, and Lg, Lg¹ and Lg² are leaving groups,
 such as halogen (e.g. Cl) or sulfonate ester (e.g. trifluoromethanesulfonate or
 methanesulfonate).

Compounds of formula (I) may be prepared according to Scheme 1.

Scheme 1



- 5 According to Scheme 1, compounds of formula (I) may be prepared by the reaction of a compound of formula (V) with an alcohol of formula (IV) under conventional conditions. Conveniently, the reaction is effected in the presence of a base, such as a trialkylamine (e.g. triethylamine), a carbonate (e.g. potassium or caesium carbonate) or hydroxide (e.g. sodium hydroxide); a solvent, such as a haloalkane (e.g. dichloromethane); and at ambient to elevated temperature, such as under reflux.

- Compounds of formula (V) may be prepared from compounds of formula (III) by derivatising the hydroxy group therein to provide a leaving group (Lg^2).
 15 Conveniently, Lg^2 is a reactive ester group, such as a sulphonic ester group, (e.g. methanesulphonate). Conveniently, the reaction is effected in the presence of a derivatising agent, such as an alkylsulphonyl halide, (e.g. methanesulphonyl chloride); a base, such as a trialkylamine base (e.g. triethylamine); a solvent

such, such as a halogenated alkane (e.g. dichloromethane); and at ambient to elevated temperature, such as ambient temperature.

5 Compounds of formula (III) may be prepared by the reaction of a compound of formula (VII) with a hydrazine of formula (VI), or a salt or hydrate thereof. Conveniently, the reaction is effected in a solvent, such as a protic solvent (e.g. acetic acid); at ambient to elevated temperature, such as ambient temperature; and optionally in the presence of an acid (e.g. acetic acid) or a base, such as a tertiary amine (e.g. triethylamine).

10

Compounds of formula (VII) may be prepared by the reaction of a compound of formula (IX) with an alcohol of formula (VIII). Conveniently, the reaction is effected in the presence of a solvent, such as a polar solvent (e.g. acetone); a base, such as an inorganic base, preferably a metal carbonate (e.g. potassium or caesium carbonate); optionally, a nucleophilic catalyst, such as sodium iodide or tetrabutylammonium iodide; and at ambient to elevated temperature, such as elevated temperature (e.g. under reflux).

15

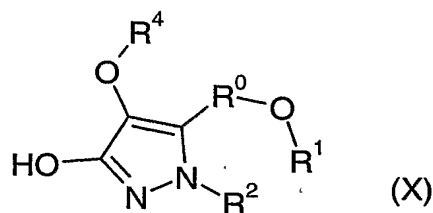
20 Ketoesters of formula (IX) are either commercially available, known in the literature, or may be prepared by conventional methods (e.g., where Lg^1 is Cl, by the chlorination of corresponding ketoesters, for instance using sulphonyl chloride).

25 According to Scheme 1, compounds of formula (I) may also be prepared by the reaction of an alcohol of formula (III) with a compound of formula (II) under conventional conditions. Conveniently, the reaction is effected in the presence of a base, such as an inorganic base, preferably a metal carbonate (e.g. potassium carbonate); optionally a solvent, such as a polar aprotic solvent (e.g. N,N-dimethylacetamide); optionally a catalyst, such as a copper(I) catalyst; and at ambient to elevated temperature, such as elevated temperature (e.g. under reflux).

30

35 According to Scheme 1, compounds of formula (I) may also be prepared by the reaction of an alcohol of formula (III) with an alcohol of formula (IV) under dehydrating conditions, such as afforded by the Mitsunobu reaction. Conveniently, the reaction is effected in the presence of an azodicarboxylate, such as diisopropylazodicarboxylate; triphenylphosphine; a solvent, such as an ether (e.g. tetrahydrofuran); and at reduced to ambient temperature, such 0°C to ambient temperature.

Compounds of formula (I) in which R^3 is halo can be prepared from a compound of formula (X)



5 under conventional conditions. Conveniently, the reaction is effected by an inorganic acid halide, such as an inorganic acid chloride (e.g. POCl_3); optionally in the presence of a solvent, such as a polar aprotic solvent (e.g. N,N-dimethylformamide); and at reduced to ambient temperature, such as ambient temperature.

10

Compounds of formula (X) may be prepared using the routes described above, *mutatis mutandis*.

15 It will be appreciated by those skilled in the art that, in many cases, it may be necessary or desirable to protect one or more sensitive functional groups, for example hydroxy groups, in the preparation of compounds of formula (I), as for example set out in Scheme 1. In particular, it may be necessary or desirable to protect the $-R^0\text{-OH}$ group of compounds of formulae (IX), (VII) and (III), and to deprotect the group prior to further transformation of a compound of formula (III).
 20 Likewise, when R^2 is H, it may be necessary or desirable to protect the pyrazole NH group of compounds of formulae (III), (V) and (I) and to deprotect the group to provide a compound of formula (I). Examples of suitable protecting groups will be apparent to the skilled person. See, for instance, 'Protecting groups in Organic Synthesis (Second Edition)' by Theodora W. Green and Peter G. M.
 25 Wuts, 1991, John Wiley and Sons (in particular pages 10 - 118, relating to protection for the hydroxyl group, and pages 309 to 405, relating to protection for the amino group, both of which describe methods for protection and subsequent deprotection), incorporated herein by reference.

30 It will be appreciated by those skilled in the art that compounds of formula (I) containing an $-\text{OH}$, $-\text{NH}-$ or $-\text{NH}_2$ group may be prepared by deprotection of the corresponding compound bearing an $-\text{OP}^1$, $-\text{NP}^1$ - or $-\text{NHP}^1$ group, respectively, wherein the group P^1 is a suitable protecting group. Such compounds bearing an $-\text{OP}^1$, $-\text{NP}^1$ - or $-\text{NHP}^1$ group may be prepared using the routes described above,
 35 *mutatis mutandis*.

It will be appreciated by those skilled in the art that, in many cases, compounds of formula (I) may be converted into other compounds of formula (I) by functional group transformations, including for example the following interconversions.

5

Compounds of formula (I) in which R^1 is phenyl substituted by C_1 - C_6 alkylsulfinyl or C_1 - C_6 alkylsulfonyl may be prepared by oxidation of the corresponding compound of formula (I) wherein R^1 is phenyl substituted by C_1 - C_6 alkylsulfanyl. The skilled artisan will appreciate that, depending on the severity of the oxidatitive conditions employed, such alkylsulfinyls of formula (I) may be partially oxidised to corresponding alkylsulfinyls, or fully oxidised to corresponding alkylsulfonyls. For the preparation of C_1 - C_6 alkylsulfinyl compounds the oxidation is, conveniently, effected in the presence of an oxidising agent, such as oxone; optionally in the presence of a moderator, such as wet alumina; a solvent, such as a haloalkane (e.g. dichloromethane); and carried out at ambient to elevated temperature, such as under reflux. For the preparation of C_1 - C_6 alkylsulfonyl compounds the oxidation is, conveniently, effected in the presence of an oxidising agent, such as oxone; a solvent, such as an aqueous alcohol (e.g. aqueous methanol); and at reduced to ambient temperature (e.g. 0°C).

20

Compounds of formula (I) in which R^2 is optionally substituted C_1 - C_6 alkyl may be prepared from compounds of formula (I) in which R^2 is H by reaction with an alkylating agent. Suitable alkylating agents include bromoacetonitrile, ethyl 4-chloroacetoacetate, methyl bromoacetate and chloroethylamine hydrochloride. Conveniently, alkylation is effected in the presence of a suitable solvent, such as an alcohol (e.g. ethanol) or a polar aprotic solvent (e.g. N,N-dimethylformamide); a base, such as a metal hydride (e.g. sodium hydride) or metal alkoxide (e.g. sodium ethoxide); and at ambient to elevated temperature, such as under reflux.

25

Compounds of formula (I) in which R^2 or R^3 contains a hydroxy group may be prepared from the corresponding compound of formula (I) in which R^2 or R^3 contains an ester group by reduction. Conveniently, the reduction is effected by a metal hydride, such as lithium aluminium hydride; in a solvent, such as an ether (e.g. diethyl ether); and at reduced temperature, such as from -78°C to 0°C .

35

Compounds of formula (I) in which R^2 or R^3 are substituted by a heterocycle of formula R^8 and R^9 may be prepared by standard heterocycle-forming reactions well known to the skilled man (see, for example, Advanced Organic Chemistry,

3rd Edition, by Gerry March or Comprehensive Heterocyclic Chemistry, A.R. Katritzky, C.W. Rees, E.F.V. Scriven, Volumes 1-11).

- 5 Compounds of formula (I) in which R^3 is $-CO_2H$ may be prepared by hydrolysis of a corresponding compound of formula (I) in which R^3 is $-CO_2R^5$. Conveniently, the reaction is effected in the presence of a solvent, such as an alcohol (e.g. aqueous ethanol), or an ether (e.g. aqueous 1,4-dioxan); and in the presence of a base, such as a metal hydroxide (e.g. sodium hydroxide). The skilled artisan will appreciate that such an acid may be converted into a primary amide by
- 10 reaction with ammonia and a suitable coupling agent, such as a carbodiimide, e.g. dicyclohexylcarbodiimide, and that such a primary amide may then be converted into a nitrile by dehydration with a suitable dehydrating agent, such as phosphoryl chloride.
- 15 Compounds of formula (I) in which R^3 is C_1-C_6 alkyl may be converted into the compounds of formula (I) in which R^3 is C_1-C_6 alkyl substituted by halo (such as bromo), by halogenation, using a suitable halogenating agent. Conveniently the reaction is effected in the presence of a solvent, such as a haloalkane (e.g. dichloromethane) and at ambient temperature. Suitable halogenating agents
- 20 include halogens (e.g. bromine) or N-halosuccinimides (e.g. N-bromsuccinimide).

Compounds of formulae (II), (IV) and (VI) and (VIII) are either commercially available, known in the literature or easily prepared by methods well known to those skilled in the art, such as those described in the Preparations hereinafter.

25

Compounds of formulae (III), (V) or (X) are key intermediates and form a further aspect of the invention.

- 30 The compounds of the invention can be administered alone, but will generally be administered in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice.

- 35 For example, the compounds of the invention can be administered orally, buccally or sublingually in the form of tablets, capsules, multi-particulates, gels, films, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications. The compounds of the invention may also be administered as fast-dispersing or fast-dissolving dosage forms or in the form of

a high energy dispersion or as coated particles. Suitable formulations of the compounds of the invention may be in coated or uncoated form, as desired.

Such solid pharmaceutical compositions, for example, tablets, may contain
5 excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate, glycine and starch (preferably corn, potato or tapioca starch), disintegrants such as sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as
10 polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

General Example

15 A formulation of the tablet could typically contain from 0.01mg to 500mg of active compound whilst tablet fill weights may range from 50mg to 1000mg. An example of a formulation for a 10mg tablet is illustrated below:

	<u>Ingredient</u>	<u>%w/w</u>
20	Compound of the invention	10.000*
	Lactose	64.125
	Starch	21.375
	Croscarmellose sodium	3.000
	Magnesium Stearate	1.500

25

* Quantity adjusted in accordance with drug activity.

The tablets are manufactured by a standard process, for example, direct
30 compression or a wet or dry granulation process. The tablet cores may be coated with appropriate overcoats.

Solid compositions of a similar type may also be employed as fillers in gelatin or HPMC capsules. Preferred excipients in this regard include lactose, starch, a
35 cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the compounds of the invention may be combined with various sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

The compounds of the invention can also be administered parenterally, for example, intravenously, intra-arterially, intraperitoneally, intrathecally, intraventricularly, intraurethrally, intrasternally, intracranially, intramuscularly or subcutaneously, or they may be administered by infusion or needleless injection techniques. For such parenteral administration they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

For oral and parenteral administration to human patients, the daily dosage level of the compounds of the invention will usually be from 0.01 to 30 mg/kg, preferably from 0.01 to 5 mg/kg (in single or divided doses).

Thus tablets or capsules of the compound of the invention may contain from 1 to 500 mg of active compound for administration singly or two or more at a time, as appropriate. The physician in any event will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention. The skilled person will appreciate that, in the treatment of certain conditions the compounds of the invention may be taken as a single dose as needed or desired.

The compounds of invention can also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomiser or nebuliser, with or without the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A [trade mark]) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA [trade mark]), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray, atomiser or nebuliser may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an

inhaler or insufflator may be formulated to contain a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

Alternatively, the compounds of the invention can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a gel, hydrogel, lotion, solution, cream, ointment or dusting powder. The compounds of the invention may also be dermally or transdermally administered, for example, by the use of a skin patch. They may also be administered by the pulmonary or rectal routes.

They may also be administered by the ocular route. For ophthalmic use, the compounds can be formulated as micronised suspensions in isotonic, pH adjusted, sterile saline, or, preferably, as solutions in isotonic, pH adjusted, sterile saline, optionally in combination with a preservative such as a benzylalkonium chloride. Alternatively, they may be formulated in an ointment such as petrolatum.

For application topically to the skin, the compounds of the invention can be formulated as a suitable ointment containing the active compound suspended or dissolved in, for example, a mixture with one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture of one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

The compounds of the invention may also be used in combination with a cyclodextrin. Cyclodextrins are known to form inclusion and non-inclusion complexes with drug molecules. Formation of a drug-cyclodextrin complex may modify the solubility, dissolution rate, bioavailability and/or stability property of a drug molecule. Drug-cyclodextrin complexes are generally useful for most dosage forms and administration routes. As an alternative to direct complexation with the drug the cyclodextrin may be used as an auxiliary additive, e.g. as a carrier, diluent or solubiliser. Alpha-, beta- and gamma-cyclodextrins are most commonly used and suitable examples are described in WO91/11172, WO94/02518 and WO98/55148.

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment.

Oral administration is preferred.

5

Included within the scope of the invention are embodiments comprising the co-administration of a compound of the invention with one or more additional therapeutic agents, and compositions containing a compound of the invention along with one or more additional therapeutic agents. Such a combination
10 therapy is especially useful for the prevention and/or treatment of infection by HIV and related retroviruses which may evolve rapidly into strains resistant to any monotherapy. Alternatively, additional therapeutic agents may be desirable to treat diseases and conditions which result from or accompany the disease being treated with the compound of the invention. For example, in the treatment of an
15 HIV or related retroviral infection, it may be desirable to additionally treat opportunistic infections, neoplasms and other conditions which occur as a result of the immuno-compromised state of the patient being treated.

Preferred combinations of the invention include simultaneous or sequential
20 treatment with a compound of the invention and one or more:

- (a) reverse transcriptase inhibitors such as abacavir, adefovir, didanosine, lamivudine, stavudine, zalcitabine and zidovudine;
- (b) non-nucleoside reverse transcriptase inhibitors such as capavirine,
25 delavirdine, efavirenz, and nevirapine;
- (c) HIV protease inhibitors such as indinivir, nelfinavir, ritonavir, and saquinavir;
- (d) CCR5 antagonists such as TAK-779 or UK-427,857;
- (e) CXCR4 antagonists such as AMD-3100;
- 30 (f) integrase inhibitors, such as L-870,810 or S-1360;
- (g) inhibitors of viral fusion such as T-20;
- (h) investigational drugs such as trizivir, KNI-272, amprenavir, GW-33908, FTC, PMPA, MKC-442, MSC-204, MSH-372, DMP450, PNU-140690, ABT-378, KNI-764, DPC-083, TMC-120 or TMC-125;
- 35 (i) antifungal agents, such as fluconazole, itraconazole or voriconazole; or
- (j) antibacterial agents, such as azithromycin.

The activity of the compounds of the invention as reverse transcriptase inhibitors may be measured using the following assay.

Inhibition of HIV-1 reverse transcriptase enzyme

Using purified recombinant HIV-1 reverse transcriptase (RT, EC, 2.7.7.49) obtained by expression in Escherichia Coli, a 96-well plate assay system is established for assaying a large number of samples using either the Poly(rA)-oligo(dT) Reverse Transcriptase [3H]-SPA enzyme assay system (Amersham NK9020) or the [3H]-flashplate enzyme assay system (NEN - SMP 103) and following the manufacturer's recommendations. The compounds are dissolved in 100% DMSO and diluted with the appropriate buffer to a 5% final DMSO concentration. The inhibitory activity is expressed in percent inhibition relative to DMSO control. The concentration at which compound inhibits reverse transcriptase by 50% is expressed as the IC₅₀ of the compound.

The compound of Examples 1 and 3, when tested according to the above procedure, had an IC₅₀ values of, respectively, 2 and 45 nanomolar.

Thus the invention provides:

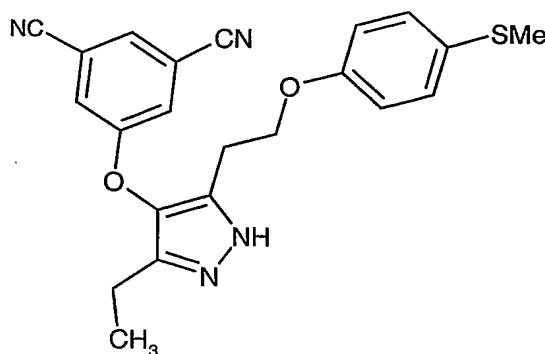
- (i) a compound of formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof;
- 5 (ii) a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof;
- (iii) a pharmaceutical composition including a compound of formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof, together with a pharmaceutically acceptable excipient, diluent or carrier;
- 10 (iv) a compound of formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, for use as a medicament;
- (v) a compound of formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, for use as a reverse transcriptase inhibitor or modulator;
- 15 (vi) a compound of formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof, for use in the treatment of an HIV or genetically-related retroviral infection, or a resulting acquired immune deficiency syndrome (AIDS);
- (vii) a use of the compound of formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament having reverse transcriptase inhibitory or modulating activity;
- 20 (viii) the use of a compound of formula (I) or of a pharmaceutically acceptable salt, solvate or composition thereof, for the manufacture of a medicament for the treatment of an HIV or genetically-related retroviral infection, or a resulting acquired immune deficiency syndrome (AIDS);
- 25 (ix) a method of treating an HIV or a genetically-related retroviral infection, or a resulting acquired immune deficiency syndrome (AIDS), comprising administering an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or composition thereof; and
- 30 (xi) certain novel intermediates disclosed herein.

The following Examples illustrate the preparation of the compounds of formula (I). The synthesis of certain intermediates used therein are described in the Preparations section that follows the Examples.

- 5 ¹H Nuclear magnetic resonance (NMR) spectra were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The following abbreviations have been used: HRMS, high
10 resolution mass spectrometry; hplc, high performance liquid chromatography; nOe, nuclear Overhauser effect; m.p., melting point; CDCl₃, deuteriochloroform; D₆-DMSO, deuterodimethylsulphoxide; CD₃OD, deuteromethanol. Where thin layer chromatography (TLC) has been used it refers to silica gel TLC using silica gel 60 F₂₅₄ plates, R_f is the distance travelled by a compound divided by the
15 distance travelled by the solvent front on a TLC plate.

EXAMPLE 1

5-[(3-Ethyl-5-{2-[4-(methylsulfany)phenoxy]ethyl}-1*H*-pyrazol-4-yl)oxy]isophthalonitrile



5

To a stirred solution of the alcohol from Preparation 10 (268mg, 0.95mmol) in tetrahydrofuran (8ml) at 0°C was added 4-(methylmercapt)phenol (200mg, 1.43mmol), triphenylphosphine (374mg, 1.43mmol) and diisopropylazodicarboxylate (275μl, 1.43mmol). The reaction was allowed to warm to room temperature and was stirred for 18 hours. The mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel eluting with dichloromethane:methanol (95:5, by volume). Column chromatography was repeated eluting with ethyl acetate and then repeated eluting with ethyl acetate:toluene (25:75, by volume) and finally repeated eluting with ethyl acetate:toluene (15:85, by volume) to give the title compound as a colourless oil (153mg).

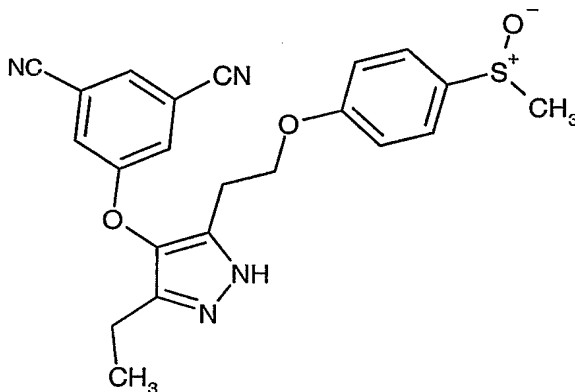
¹H NMR (400MHz, CDCl₃): δ = 1.20 (t, 3H), 2.44 (s, 3H), 2.50 (q, 2H), 2.97 (t, 2H), 4.15 (t, 2H), 6.71 (d, 2H), 7.20 (d, 2H), 7.38 (s, 2H), 7.53 (s, 1H).

20

LRMS (atmospheric chemical ionisation): m/z [MH⁺] 405.

EXAMPLE 2

5-[(3-Ethyl-5-{2-[4-(methylsulfinyl)phenoxy]ethyl}-1H-pyrazol-4-yl)oxy]isophthalonitrile



5

Wet alumina was prepared by adding water (1ml) to Brockman grade I alumina (5g). A sample of this material (160mg) was added to a stirred solution of the sulfide from Example 1 (106mg, 0.16mmol) in dichloromethane (1ml), followed by oxone (98mg, 0.16mmol). The reaction mixture was heated at reflux for 45 minutes, before being filtered. The solids were washed with dichloromethane (10ml) and the combined organics were concentrated under reduced pressure. The crude product mixture was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (100:0, 98:2 and 96:4, by volume) to give the title compound as a colourless oil (25mg).

15

^1H NMR (400MHz, CDCl_3): δ = 1.19 (t, 3H), 2.50 (q, 2H), 2.71 (s, 3H), 2.99 (t, 2H), 4.23 (t, 2H), 6.92 (d, 2H), 7.39 (s, 2H), 7.55 (s, 1H), 7.56 (d, 2H).

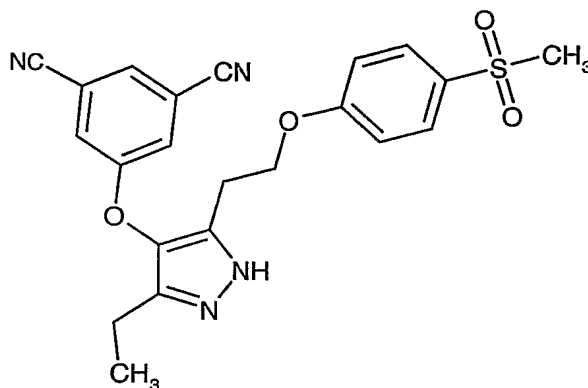
LRMS (atmospheric pressure chemical ionisation): m/z $[\text{MH}^+]$ 421

Accurate Mass: Found: 421.1323 $[\text{MH}^+]$; $\text{C}_{22}\text{H}_{21}\text{N}_4\text{O}_3\text{S}$ requires 421.1329 $[\text{MH}^+]$.

20

EXAMPLE 3

5-[(3-Ethyl-5-{2-[4-(methylsulfonyl)phenoxy]ethyl}-1*H*-pyrazol-4-yl)oxy]isophthalonitrile



5

To a stirred solution of the sulfide from Example 1 (90mg, 0.22mmol) in methanol (2ml) at 0°C was added a solution of oxone (205mg, 0.33mmol) in water (2ml). The viscous suspension was further diluted with methanol (2ml). After 4 hours
10 the reaction mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane (20ml) and water (20ml). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product mixture was purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (50:50, by volume) to give the title compound
15 compound (70mg) as a white powder, m.p. 88-90°C.

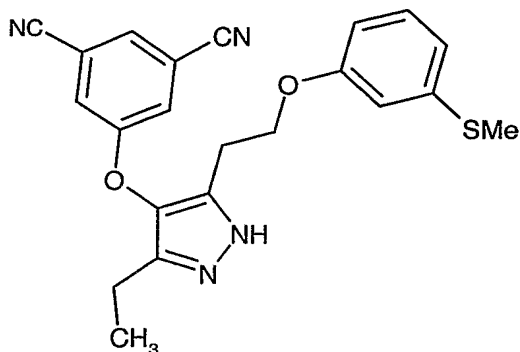
¹H NMR (400MHz, CDCl₃): δ = 1.20 (t, 3H), 2.51 (q, 2H), 3.00 (t, 2H), 3.03 (s, 3H), 4.27 (t, 2H), 6.92 (d, 2H), 7.39 (s, 2H), 7.56 (s, 1H), 7.84 (d, 2H).

LRMS (atmospheric pressure chemical ionisation): m/z [MH⁺] 437

20 Microanalysis: Found: C, 60.17; H, 4.60; N, 12.73. C₂₂H₂₀N₄O₄S requires C, 60.54; H, 4.62; N, 12.84%.

EXAMPLE 4

5-[(3-Ethyl-5-{2-[3-(methylsulfanyl)phenoxy]ethyl}-1*H*-pyrazol-4-yl)oxy]isophthalonitrile



5

To a stirred solution of the alcohol from Preparation 10 (395mg, 1.40mmol) in tetrahydrofuran (14ml) at 0°C was added 3-(methylmercaptophenol) (196mg, 1.40mmol), triphenylphosphine (367mg, 1.40mmol) and diethylazodicarboxylate (276μl, 1.60mmol). The reaction was allowed to warm to room temperature and was stirred for 18 hours. The mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel eluting with pentane:ethyl acetate (9:1, 5:1 and 3:1 by volume). Column chromatography was repeated eluting with dichloromethane:acetonitrile (100:0, 99:1, 98:2 and 97:3 by volume) to give the title compound as a colourless oil (207mg, approximately 60% pure w/w) which was contaminated with triphenylphosphine oxide and the reduced diethylazodicarboxylate.

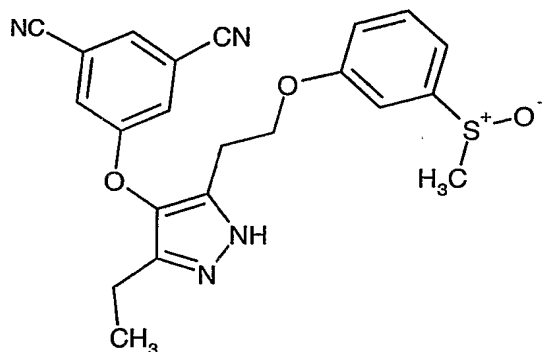
¹H NMR (400MHz, CDCl₃): δ = 1.16 (t, 3H), 2.45 (s, 3H), 2.48 (q, 2H), 2.96 (t, 2H), 4.16 (t, 2H), 6.53 (d, 1H), 6.62 (s, 1H), 6.81 (s, 1H), 7.13 (t, 1H), 7.35 (s, 2H), 7.53 (s, 1H).

20

LRMS (atmospheric chemical ionisation): m/z [MH⁺] 405.

EXAMPLE 5

5-[(3-Ethyl-5-{2-[3-(methylsulfinyl)phenoxy]ethyl}-1H-pyrazol-4-yl)oxy]isophthalonitrile



5

Wet alumina was prepared by adding water (1ml) to Brockman grade I alumina (5g). A sample of this material (320mg) was added to a stirred solution of the sulfide from Example 4 (217mg, 0.32mmol) in dichloromethane (2ml), followed by oxone (196mg, 0.32mmol). The reaction mixture was heated at reflux for 45 minutes, before being filtered. The solids were washed with dichloromethane (10ml) and the combined organics were concentrated under reduced pressure. The crude product mixture was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (100:0, 98:2 and 96:4, by volume) to give the title compound as a colourless oil (69mg).

^1H NMR (400MHz, CDCl_3): δ = 1.19 (t, 3H), 2.12 (q, 2H), 2.73 (s, 3H), 2.99 (t, 2H), 4.27 (t, 2H), 6.88 (d, 1H), 7.10 (d, 1H), 7.20 (m, 1H), 7.37 (t, 1H), 7.39 (s, 2H), 7.54 (s, 1H).

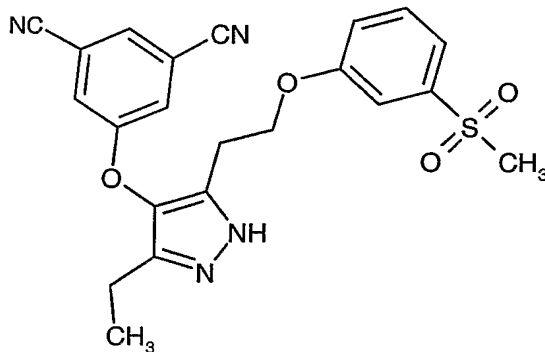
LRMS (atmospheric pressure chemical ionisation): m/z [MH^+] 421

Accurate Mass: Found: 421.1330 [MH^+]; $\text{C}_{22}\text{H}_{21}\text{N}_4\text{O}_3\text{S}$ requires 421.1329 [MH^+].

20

EXAMPLE 6

5-[(3-Ethyl-5-{2-[3-(methylsulfonyl)phenoxy]ethyl}-1*H*-pyrazol-4-yl)oxy]isophthalonitrile



5

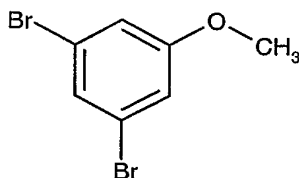
To a stirred solution of the sulfoxide from Example 5 (34mg, 0.08mmol) in methanol (1ml) was added a solution of oxone (49mg, 0.08mmol) in water (1ml). After 2 hours the reaction mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane (5ml) and water (5ml). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product mixture was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (100:0, 99:1 then 98:2, by volume) to give the title compound as a colourless oil (12mg).

15

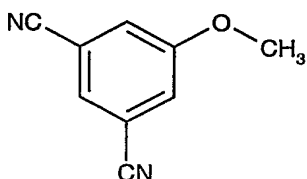
¹H NMR (400MHz, CDCl₃): δ = 1.21 (t, 3H), 2.52 (q, 2H), 3.01 (t, 2H), 3.06 (s, 3H), 4.27 (t, 2H), 7.08 (d, 1H), 7.34 (t, 1H), 7.41 (s, 2H), 7.46 (t, 1H), 7.53 (m, 1H), 7.57 (s, 1H).

LRMS (atmospheric pressure chemical ionisation): m/z [MH⁺] 437

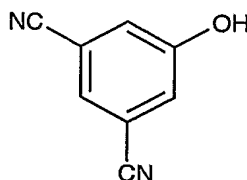
20 Accurate Mass: Found: 437.1279 [MH⁺]; C₂₂H₂₁N₄O₃S requires 421.1278 [MH⁺].

PREPARATION 1**1,3-Dibromo-5-methoxybenzene**

- 5 Sodium methoxide (8.80ml of a 4.5M solution in methanol, 39.6mmol) was added dropwise to a stirred solution of 3,5-dibromofluorobenzene (5.00g, 19.0mmol) in *N,N*-dimethylformamide (95ml) at 0°C under nitrogen. The reaction was allowed to warm to room temperature, stirred for 1 hour and then concentrated under reduced pressure. The residue was dissolved in ether (500ml) and the resulting
- 10 solution was washed with water (3x300ml) and brine (300ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure to provide the title compound (5.13g) as a white solid.
- ¹H-NMR (300MHz, CDCl₃): δ = 3.79 (s, 3H), 7.00 (s, 2H), 7.26 (s, 1H).
- LRMS (thermospray): m/z [MH⁺] 266.
- 15 Microanalysis: Found: C, 31.56; H, 2.29. C₇H₆OBr₂ requires C, 31.62; H, 2.27%.

PREPARATION 2**3,5-Dicyanomethoxybenzene**

- 20 Tris(dibenzylideneacetone)dipalladium(0) (6.53g, 7.15mmol) was added in one portion to a stirred solution of the bromide of Preparation 1 (38.0g, 143mmol), 1,1'-bis(diphenylphosphino)ferrocene (9.3g, 16.8mmol) and zinc cyanide (20.0g, 172mmol) in *N,N*-dimethylformamide (300ml) at room temperature under
- 25 nitrogen. The reaction was heated at 100°C for 14 hours and cooled to room temperature. Water (1500ml) was added and the mixture was extracted with ethyl acetate (3x500ml). The combined organics were filtered and the filtrate was washed with water (500ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The resulting solid was triturated with
- 30 toluene (1000ml) to provide the title compound (18.0g) as a tan solid.
- ¹H-NMR (300MHz, CDCl₃): δ = 3.83 (3H, s), 7.31 (2H, s), 7.48 (1H, s).

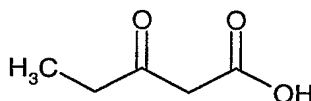
PREPARATION 33,5-Dicyanohydroxybenzene

5

The nitrile of Preparation 2 (9.60g, 60.7mmol) was added portionwise to a stirred suspension of aluminium trichloride (32.4g, 243mmol) in dichloromethane (250ml) at 0°C under nitrogen. The suspension was heated to 45°C and stirred for 6 days. The reaction was cooled to room temperature and cautiously poured onto ice (450ml). Concentrated hydrochloric acid (450ml) was added dropwise and the resulting suspension was stirred for 10 minutes at room temperature. The resulting solid was collected by filtration, washed with water and dried over phosphorus pentoxide to provide the title compound (7.83g) as a tan solid containing approximately 10 % starting material by ¹H-NMR and microanalysis.

¹H-NMR (400MHz, CDCl₃): δ = 7.36 (m, 2H), 7.56 (m, 1H).

15

PREPARATION 43-Oxopentanoic acid

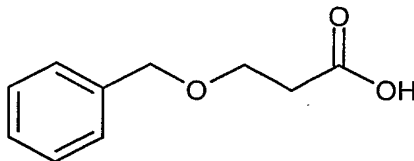
20

Sodium hydroxide (54g, 1.35mol) was added portionwise to a solution of 3-oxopentanoic acid methyl ester (80g, 0.62mol) in tetrahydrofuran (300ml) and water (300ml) at 0°C. The reaction was allowed to warm to room temperature and was stirred for 18 hours. The reaction mixture was washed with diethylether (500ml) and the aqueous phase was acidified to pH1 at 0°C with concentrated hydrochloric acid (140ml). The aqueous phase was extracted with dichloromethane (2x300ml) and the combined organic extracts dried over magnesium sulphate and concentrated under reduced pressure to provide the title compound (44g) as a white solid.

25

¹H NMR (400MHz, CDCl₃): δ = 1.12 (t, 3H), 2.59 (q, 2H), 3.49 (s, 2H).

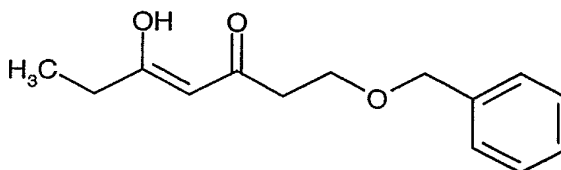
30

PREPARATION 53-(Benzyloxy)propanoic acid

- 5 Sodium metal (249mg, 10.8mmol) was added to benzyl alcohol (30g, 278mmol) at room temperature under nitrogen and the reaction was stirred for 30 minutes. Methyl acrylate (25.9ml, 259mmol) was then added dropwise and the reaction was stirred at room temperature for 18h. After quenching with saturated aqueous ammonium chloride solution (200ml) the mixture was extracted with
- 10 ethyl acetate (2x300ml) and the combined organic extracts were washed with brine (100ml), dried over magnesium sulphate and concentrated under reduced pressure. The residual oil was dissolved in ethanol (300ml) and 1M aqueous sodium hydroxide solution (300ml) was added dropwise. After 3 hours the ethanol was removed under reduced pressure and the aqueous residue was
- 15 washed with dichloromethane (200ml). The aqueous phase was then acidified with 2N aqueous hydrochloric acid (150ml), extracted with dichloromethane (2x250ml) and the combined organic extracts were dried over magnesium sulphate and concentrated under reduced pressure. The residual oil was dissolved in 10% aqueous potassium carbonate solution (300ml), washed with
- 20 diethylether (300ml) and the aqueous phase was acidified to pH1 using concentrated hydrochloric acid. The mixture was then extracted with dichloromethane (2x300ml) and the combined organic extracts were dried over magnesium sulphate and concentrated under reduced pressure to provide the title compound (44.4g) as a colourless oil.
- 25 ¹H NMR (300MHz, CDCl₃): δ = 2.67 (t, 2H), 3.89 (t, 2H), 4.58 (s, 2H), 7.18 (m, 5H).

PREPARATION 6(4Z)-1-(Benzyloxy)-5-hydroxy-4-hepten-3-one

30



A suspension of magnesium turnings (1.74g, 71.6mmol) in methanol (85ml) was heated at reflux under nitrogen for 1.5 hours, cooled to room temperature and

the β -keto acid from Preparation 4 (16.6g, 143mmol) was added. The reaction was stirred for 1.5 hours and the solvent was removed under reduced pressure to give the magnesium salt of the acid as a white solid. Meanwhile, the acid from Preparation 5 (12.9g, 71.6mmol) was dissolved in N,N'-dimethylformamide (150ml) and carbonyldiimidazole (12.8g, 78.8mmol) was added portionwise under nitrogen at room temperature. This was stirred for 1 hour and then the magnesium salt from above was added as a solution in N,N'-dimethylformamide (50ml). Evolution of gas was noted, and the reaction was allowed to stir at room temperature for 18 hours. The mixture was concentrated under reduced pressure and the residual orange oil was dissolved in dichloromethane (300ml), washed with 0.5M aqueous hydrochloric acid (250ml) containing methanol (10ml) and the aqueous phase was separated and extracted with dichloromethane (2x300ml). The combined organic extracts were washed with brine (300ml) containing methanol (20ml), dried over magnesium sulphate, filtered and concentrated under reduced pressure. The residual orange oil was purified by flash chromatography on silica gel eluting with cyclohexane:ethyl acetate (80:20, by volume) to provide the title compound (12.0g) as an orange oil.

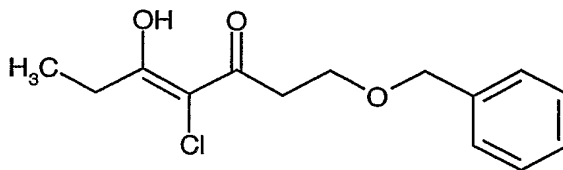
^1H NMR (400MHz, CDCl_3): δ = 1.17 (t, 3H), 2.33 (q, 2H), 2.58 (t, 2H), 3.76 (t, 2H), 4.53 (s, 2H), 5.57 (s, 1H), 7.13 (m, 5H).

LRMS (electrospray) : m/z [MNa^+] 257.

Microanalysis: Found C, 71.77; H, 7.74. $\text{C}_{14}\text{H}_{18}\text{O}_3$ requires C, 71.76; H, 7.69%.

PREPARATION 7

(4E)-1-(Benzyloxy)-4-chloro-5-hydroxy-4-hepten-3-one



Chlorotrimethylsilane (10ml, 51.3mmol) was added to a solution of the enol from Preparation 6 (4.0g, 17.1mmol) in acetonitrile (25ml) under nitrogen at 0°C. Dimethylsulfoxide (3.6ml, 51.3mmol) followed by tert-butylammonium bromide (275mg, 0.85mmol) were then added and the reaction was stirred at 0°C for 2 hours. The mixture was diluted with water (100ml), extracted with diethylether (100ml) and the organic phase was washed with brine (50ml), dried over magnesium sulphate and concentrated under reduced pressure. The residual pink oil was purified by flash chromatography on silica gel eluting with

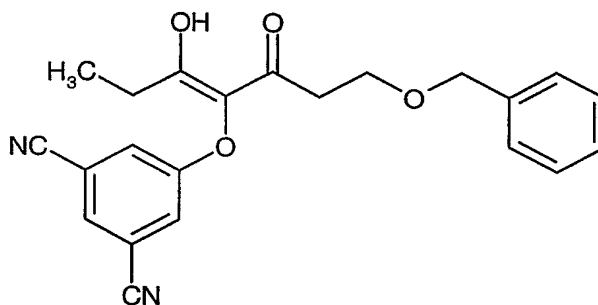
cyclohexane:ethyl acetate (80:20, by volume) to provide the title compound (3.76g) as a pink oil.

^1H NMR (400MHz, CDCl_3): δ = 1.17 (t, 3H), 2.62 (q, 2H), 2.96 (t, 2H), 3.79 (t, 2H), 4.57 (s, 2H), 7.12 (m, 5H), 15.49 (s, 1H).

5 LRMS (electrospray) : m/z [MNa^+] 291.

PREPARATION 8

5-(((1E)-1-[3-(Benzyloxy)propanoyl]-2-hydroxy-1-butenyl}oxy)isophthalonitrile

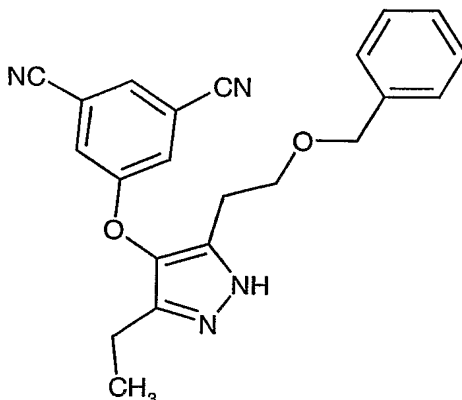


10

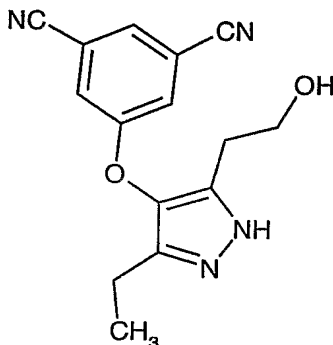
To a stirred solution of the chlorodiketone from Preparation 7 (1.5g, 5.6mmol) in acetone (30ml) was added the phenol from Preparation 3 (0.8g, 5.6mmol) followed by cesium carbonate (1.8g, 5.6mmol). The reaction mixture was heated at reflux for 2 hours and was then allowed to cool to room temperature. The reaction mixture was concentrated under reduced pressure and the residue was diluted with between water (50ml), 2N aqueous hydrochloric acid (50ml) and extracted with dichloromethane (2x100ml). The combined organic components were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude product mixture was purified by column chromatography on silica gel eluting with pentane:ethyl acetate (90:10 then 80:20, by volume) to provide the title compound (0.9g) as a yellow oil.

^1H NMR (400MHz, CDCl_3): δ = 1.08 (t, 3H), 2.29 (q, 2H), 2.58 (t, 2H), 3.73 (t, 2H), 4.44 (s, 2H), 7.12 (m, 5H), 7.45 (s, 2H), 7.57 (s, 1H), 14.51 (s, 1H).

25 LRMS (atmospheric pressure chemical ionisation): m/z [M-H^+] 375.

PREPARATION 95-({5-[2-(Benzyloxy)ethyl]-3-ethyl-1H-pyrazol-4-yl}oxy)isophthalonitrile

- 5 To a stirred solution of the diketone from Preparation 8 (0.85g, 2.3mmol) in acetic acid (20ml) was added hydrazine hydrate (0.17ml, 3.4mmol). After 18 hours the reaction mixture was concentrated under reduced pressure to give a yellow oil (0.85g) which was used without further purification. An analytical sample of the product was purified by preparative HPLC using a Develosil combi-rp C30
- 10 50x4.6mm 3 μ m column eluting with a solvent gradient of 5:95 0.1% aqueous trifluoroacetic acid in water:acetonitrile to provide the title compound as a colourless oil.
- ^1H NMR (400MHz, CDCl_3): δ = 1.18 (t, 3H), 2.44 (q, 2H), 2.77 (t, 2H), 3.63 (t, 2H), 4.52 (s, 2H), 7.30 (m, 7H), 7.55 (s, 1H).
- 15 LRMS (electrospray) : m/z [MH^+] 231, [MNa^+] 253.

PREPARATION 105-([3-Ethyl-5-(2-hydroxyethyl)-1H-pyrazol-4-yl]oxy)isophthalonitrile

20

Iron(III)chloride (3.7g, 23mmol) was added to a solution of the crude pyrazole from Preparation 9 (0.85g, 2.3mmol) in dichloromethane (30ml) at room temperature. After stirring for 20 minutes the mixture was diluted with

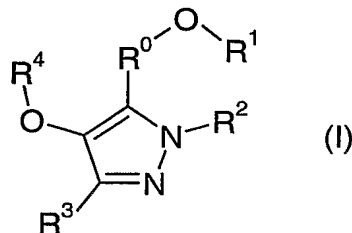
dichloromethane (100ml) and washed with water (50ml). The separated aqueous phase was washed with dichloromethane (100ml) and the combined organic components were dried over magnesium sulphate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with dichloromethane:methanol (98:2 changing to 95:5, by volume) to provide the title compound (0.50g) as a white solid.

^1H NMR (400MHz, CDCl_3): δ = 1.19 (t, 3H), 2.51 (q, 2H), 2.69 (t, 2H), 3.88 (t, 2H), 7.40 (s, 2H), 7.59 (s, 1H).

LRMS (electrospray): m/z [MH^+] 283.

CLAIMS

1. A compound of formula (I)



or a pharmaceutically acceptable salt, solvate or derivative thereof, wherein:

R⁰ is absent or C₁-C₆ alkylene;

10

R¹ is phenyl substituted by -SO_yR⁵, (C₁-C₆ alkylene)-SO_yR⁵, -SO_yCF₃, (C₁-C₆ alkylene)-SO_yCF₃, -CO₂R⁵, -(C₀-C₆ alkylene)-CO₂R⁵, OCF₃, a five or six-membered aromatic heterocyclic group containing (i) from 1 to 4 nitrogen heteroatom(s) or (ii) 1 or 2 nitrogen heteroatom(s) and 1 oxygen or 1 sulphur heteroatom (said heterocyclic group being optionally substituted by halo, oxo, -CN, -COR⁵, -CO₂R⁵, -CONR⁵R⁵, -SO_yR⁵, -SO_yCF₃, -SO₂NR⁵R⁵, -NR⁵SO₂R⁵, -OR⁵, -OCF₃, -NR⁵R⁵, -(C₁-C₆ alkylene)-NR⁵R⁵, C₁-C₆ alkyl, fluoro(C₁-C₆)alkyl or C₃-C₇ cycloalkyl); or, when R⁰ is C₁-C₆ alkylene, R¹ may also be a five or six-membered aromatic heterocyclic group containing (i) from 1 to 4 nitrogen heteroatom(s) or (ii) 1 or 2 nitrogen heteroatom(s) and 1 oxygen or 1 sulphur heteroatom or (iii) 1 or 2 oxygen or sulphur heteroatom(s), said heterocyclic group being optionally substituted by halo, oxo, -CN, -COR⁵, -CONR⁵R⁵, -SO₂NR⁵R⁵, -NR⁵SO₂R⁵, -OR⁵, -OR¹¹, -NR⁵R⁵, -(C₁-C₆ alkylene)-NR⁵R⁵, R⁷ or R¹¹; said phenyl being optionally additionally substituted by halo, -CN, -COR⁵, -CONR⁵R⁵, -SO₂NR⁵R⁵, -NR⁵SO₂R⁵, -OR⁵, -NR⁵R⁵, -(C₁-C₆ alkylene)-NR⁵R⁵, C₁-C₆ alkyl, halo(C₁-C₆)alkyl or C₃-C₇ cycloalkyl;

20

25

30

R² is H, C₁-C₆ alkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkenyl, phenyl, benzyl, R⁸ or R⁹, said C₁-C₆ alkyl, C₃-C₇ cycloalkyl, phenyl and benzyl being optionally substituted by halo, -OR⁵, -OR¹⁰, -CN, -CO₂R⁷, -OCONR⁵R⁵, -CONR⁵R⁵, -C(=NR⁵)NR⁵OR⁵, -CONR⁵NR⁵R⁵, -NR⁶R⁶, -NR⁵R¹⁰, -NR⁵COR⁵, -NR⁵COR⁸, -NR⁵COR¹⁰, -NR⁵CO₂R⁵, -NR⁵CONR⁵R⁵, -SO₂NR⁵R⁵, -NR⁵SO₂R⁵, -NR⁵SO₂NR⁵R⁵, R⁸ or R⁹;

R^3 is H, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, phenyl, benzyl, halo, -CN, -OR⁷, -CO₂R⁵, -CONR⁵R⁵, R⁸ or R⁹, said C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, phenyl and benzyl being optionally substituted by halo, -CN, -OR⁵, -CO₂R⁵, -CONR⁵R⁵, -OCONR⁵R⁵, -NR⁵CO₂R⁵, -NR⁶R⁶, -NR⁵COR⁵, -SO₂NR⁵R⁵, -NR⁵CONR⁵R⁵, -NR⁵SO₂R⁵, R⁸ or R⁹;

R^4 is phenyl, naphthyl or pyridyl, each being optionally substituted by R⁸, halo, -CN, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_3 - C_7 cycloalkyl, C_1 - C_6 alkoxy, -CONR⁵R⁵, OR¹¹, SO_xR⁶, O-(C_1 - C_6 alkylene)-CONR⁵R⁵, O-(C_1 - C_6 alkylene)-NR⁵R⁵, or O-(C_1 - C_6 alkylene)-OR⁶;

each R⁵ is independently either H, C_1 - C_6 alkyl or C_3 - C_7 cycloalkyl or, when two R⁵ groups are attached to the same nitrogen atom, those two groups taken together with the nitrogen atom to which they are attached represent azetidiny, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl or morpholinyl, said azetidiny, pyrrolidinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl and morpholinyl being optionally substituted by C_1 - C_6 alkyl or C_3 - C_7 cycloalkyl;

each R⁶ is independently either H, C_1 - C_6 alkyl or C_3 - C_7 cycloalkyl;

R⁷ is C_1 - C_6 alkyl or C_3 - C_7 cycloalkyl;

R⁸ is a five or six-membered, aromatic heterocyclic group containing (i) from 1 to 4 nitrogen heteroatom(s) or (ii) 1 or 2 nitrogen heteroatom(s) and 1 oxygen or 1 sulphur heteroatom or (iii) 1 or 2 oxygen or sulphur heteroatom(s), said heterocyclic group being optionally substituted by halo, oxo, -CN, -COR⁵, -CONR⁵R⁵, -SO₂NR⁵R⁵, -NR⁵SO₂R⁵, -OR⁵, -NR⁵R⁵, -(C_1 - C_6 alkylene)-NR⁵R⁵, C_1 - C_6 alkyl, fluoro(C_1 - C_6)alkyl or C_3 - C_7 cycloalkyl;

R⁹ is a four to seven-membered, saturated or partially unsaturated heterocyclic group containing (i) 1 or 2 nitrogen heteroatom(s) or (ii) 1 nitrogen heteroatom and 1 oxygen or 1 sulphur heteroatom or (iii) 1 oxygen or sulphur heteroatom, said heterocyclic group being optionally substituted by oxo, C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, -SO₂R⁵, -CONR⁵R⁵, -COOR⁵, -CO-(C_1 - C_6 alkylene)-OR⁵ or -COR⁵ and optionally substituted on a carbon atom which is not adjacent to a heteroatom by halo, -OR⁵, -NR⁵R⁵, -NR⁵COR⁵, -NR⁵COOR⁵, -NR⁵CONR⁵R⁵, -NR⁵SO₂R⁵ or -CN;

R¹⁰ is C₁-C₆ alkyl substituted by R⁸, R⁹, -OR⁵, -CONR⁵R⁵, -NR⁵COR⁵ or -NR⁵R⁵;

R¹¹ is phenyl optionally substituted by halo, -CN, -COR⁵, -CONR⁵R⁵, -SO₂NR⁵R⁵,
-NR⁵SO₂R⁵, -OR⁵, -NR⁵R⁵, -(C₁-C₆ alkylene)-NR⁵R⁵, C₁-C₆ alkyl, halo(C₁-C₆)alkyl
5 or C₃-C₇ cycloalkyl; and

x and y are independently 0, 1 or 2.

2. A pharmaceutical composition including a compound of formula (I) or a
10 pharmaceutically acceptable salt, solvate or derivative thereof together with one
or more pharmaceutically acceptable excipients, diluents or carriers.

3. A pharmaceutical composition according to claim 2 including one or more
15 additional therapeutic agents.

4. A compound of formula (I) or a pharmaceutically acceptable salt, solvate or
derivative thereof, or a pharmaceutical composition according to claim 2 or 3, for
use as a medicament.

5. A compound of formula (I) or a pharmaceutically acceptable salt, solvate or
20 derivative thereof, or a pharmaceutical composition according to claim 2 or 3, for
use as a reverse transcriptase inhibitor or modulator.

6. A compound of formula (I) or a pharmaceutically acceptable salt, solvate or
25 derivative thereof, or a pharmaceutical composition according to claim 2 or 3, for
use in the treatment of an HIV or genetically-related retroviral infection, or a
resulting acquired immune deficiency syndrome (AIDS).

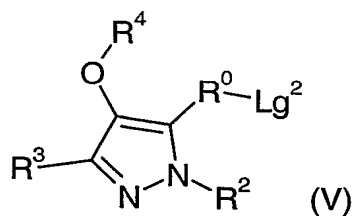
7. Use of a compound of formula (I) or a pharmaceutically acceptable salt,
30 solvate or derivative thereof, or a pharmaceutical composition according to claim
2 or 3, for the manufacture of a medicament having reverse transcriptase
inhibitory or modulating activity.

8. Use of a compound of formula (I) or a pharmaceutically acceptable salt,
35 solvate or derivative thereof, or a pharmaceutical composition according to claim
2 or 3, for the manufacture of a medicament for the treatment of an HIV or
genetically-related retroviral infection, or a resulting acquired immune deficiency
syndrome (AIDS).

9. A method of treating an HIV or a genetically-related retroviral infection, or a resulting acquired immune deficiency syndrome (AIDS), comprising administering an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or derivative thereof, or a pharmaceutical composition according to claim 2 or 3.

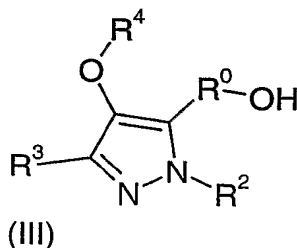
10. A process for preparing the compound of formula (I) or a salt, solvate or pharmaceutically acceptable derivative thereof, which comprises:

- 10 (A) reaction of a compound of formula (V)



with an alcohol of formula (IV), R¹-OH (IV), under conventional conditions;

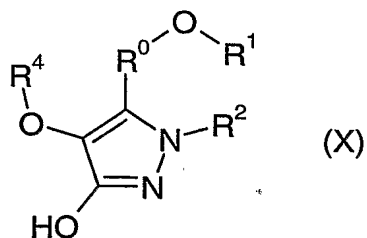
- 15 (B) reaction of an alcohol of formula (III)



- 20 with a compound of formula (II), Lg-R¹ (II), under conventional conditions;

- (C) reaction of a compound of formula (III) with an alcohol of formula (IV) under dehydrating conditions;

- (D) for the preparation of a compound of formula (I) in which R^3 is halo, halogenating a compound of formula (X)



5

under conventional conditions;

- (E) interconversion of a compound of formula (I) into another compound of formula (I); or

10

- (F) deprotecting a protected derivative of compound of formula (I); and

optionally converting a compound of formula (I) prepared by any one of processes (A) to (F) into pharmaceutically acceptable salt, solvate or derivative thereof.

15

11. A compound of formulae (III), (V) or (X).

INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/JP 03/04214

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D231/18 A61K31/4166

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; STANOVNIK, B. ET AL: "Product class 1: pyrazoles" retrieved from STN Database accession no. 139:214344 XP002265853 compound with RN 591233-74-8 abstract & SCIENCE OF SYNTHESIS (2002), 12, 15-225,	11
X,P	WO 02 085860 A (PRICE DAVIS ANTHONY ;PFIZER LTD (GB); JONES LYN HOWARD (GB); MOWBR) 31 October 2002 (2002-10-31) claims 1,35,40 examples 102,135,147-154 --- -/--	1,4,7, 9-11

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

19 December 2003

Date of mailing of the international search report

13/01/2004

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INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/JP 03/04214

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02 30907 A (HOFFMANN LA ROCHE) 18 April 2002 (2002-04-18) cited in the application claim 1 -----	1,4,7,9
Y	WO 02 04424 A (CORBAU ROMUALD GASTON ;PFIZER LTD (GB); WOOD ANTHONY (GB); MOWBRAY) 17 January 2002 (2002-01-17) cited in the application claims 1,32 -----	1,4,7,9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 03/04214

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: 11
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 9 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 9

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Continuation of Box I.2

Claims Nos.: 11

Present claim 11 refers to the compound of formula V according to claim 10. The said compound of formula V bears a substituent LG2 for which no definition is given neither in claim 10 nor in claim 11 or in any other of the present claims. Thus, a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of claim 11 impossible. Consequently, the search has been limited to the definition of LG2 given on page 10 of the present description, namely to LG2 being a sulphonic ester group.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat

Application No

PCT/IB 03/04214

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 02085860	A	31-10-2002	WO 02085860 A1	31-10-2002
			US 2003100554 A1	29-05-2003
WO 0230907	A	18-04-2002	AU 2165102 A	22-04-2002
			BR 0114483 A	01-07-2003
			CA 2423515 A1	18-04-2002
			WO 0230907 A1	18-04-2002
			EP 1326843 A1	16-07-2003
			NO 20031615 A	23-05-2003
			US 2003018197 A1	23-01-2003
WO 0204424	A	17-01-2002	AU 6776601 A	21-01-2002
			BR 0112252 A	02-09-2003
			CA 2415492 A1	17-01-2002
			EP 1299361 A1	09-04-2003
			WO 0204424 A1	17-01-2002
			US 2002032184 A1	14-03-2002